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Modulating exercise-induced hormesis: does less equal more?

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ABSTRACT

Hormesis encompasses the notion that low levels of stress stimulate or upregulate existing cellular and molecular pathways that improve the capacity of cells and organisms to withstand greater stress. This notion underlies much of what we know about how exercise conditions the body and induces long-term adaptations. During exercise, the body is exposed to various forms of stress, including thermal, metabolic, hypoxic, oxidative, and mechanical stress. These stressors activate biochemical messengers, which in turn activate various signaling pathways that regulate gene expression and adaptive responses. Historically, antioxidant supplements, nonsteroidal anti-inflammatory drugs, and cryotherapy have been favored to attenuate or counteract exercise-induced oxidative stress and inflammation. However, reactive oxygen species and inflammatory mediators are key signaling molecules in muscle, and such strategies may mitigate adaptations to exercise. Conversely, withholding dietary carbohydrate and restricting muscle blood flow during exercise may augment adaptations to exercise. In this review article, we combine, integrate, and apply knowledge about the fundamental mechanisms of exercise adaptation. We also critically evaluate the rationale for using interventions that target these mechanisms under the overarching concept of hormesis. There is currently insufficient evidence to establish whether these treatments exert dose-dependent effects on muscle adaptation. However, there appears to be some dissociation between the biochemical/molecular effects and functional/performance outcomes of some of these treatments. Although several of these treatments influence common kinases, transcription factors and proteins, it remains to be determined if these interventions complement or negate each other, and whether such effects are strong enough to influence adaptations to exercise.

Key words: adaptation, stress, preconditioning.

INTRODUCTION

Hormesis refers to 'a process in which a low dose of a chemical agent or environmental factor that is damaging at high doses induces an adaptive beneficial effect on the cell or organism' (127). The concept of hormesis first originated in the 16th century from the musings of the Swiss physician and alchemist Paracelcus, who proposed that, "Solely the dose determines that a thing is not a poison" (15). The term 'hormesis' itself was first coined in 1943 by Southam and Ehrlich to explain their observation that a natural antibiotic in cedar wood inhibited the growth of wood-decaying fungi but had the opposite effect at low doses (204). Subsequently, the pioneering endocrinologist Hans Selye applied this notion to understanding how biological systems respond to and tolerate environmental stress (194).

Hormesis encompasses the fundamental concepts of 'conditioning' and 'adaptation'. The concept of conditioning was first recognized following observations that repeated, brief hypoxic exposure markedly reduced damage to the heart during subsequent myocardial infarction (141). We now accept that exposure to an agent conditions the system to respond in some manner (22). The concept of adaptation was originally recognized following experiments demonstrating that constant exposure of *Escherichia coli* to mutagens allowed each bacterium to handle mutagens more efficiently and to develop resistance to mutagenesis (184). Conditioning and adaptation are closely related, are considered to be synonymous, and are often used interchangeably. In essence, conditioning/adaptation captures the notion that low levels of stress stimulate or upregulate existing cellular and molecular pathways that improve the capacity of cells and organisms to withstand greater stress (22).

The notion of hormesis underlies much of what we know about how exercise conditions the body and induces long-term adaptation (32). However, hormesis was explicitly introduced into the lexicon of exercise physiology only relatively recently (175). On a gross population level, the dose–response nature of hormesis most likely explains why moderate levels of physical activity reduce the risk of illness and mortality, whereas excessive physical activity increases such risks (5, 103, 147).

During exercise, the body is exposed to various homeostatic perturbations, including thermal, metabolic, hypoxic, oxidative, and mechanical stress. These perturbations stimulate the release of biochemical messengers such as reactive oxygen and nitrogen species (RONS), Ca^{2+}, growth factors, cytokines, and eicosanoids. These messengers then activate signaling pathways including (but not limited to) various protein kinases, phosphatases, and deacetylases, which in turn regulate the molecular machinery controlling gene expression that elicits the appropriate adaptive responses (40). Through these signaling pathways, acute production of RONS and inflammatory mediators can ultimately promote adaptations in skeletal muscle such as mitochondrial biogenesis and remodeling/hypertrophy (53, 124, 125, 169, 197). Conversely, prolonged production of RONS and inflammatory mediators can activate proteolytic pathways, impede protein synthesis, and overwhelm endogenous defense mechanisms, which cause adverse effects such as muscle atrophy/weakness (37, 56, 62, 106, 203, 206). This dichotomy between the acute and chronic effects of certain physiological stimuli is important to consider within the context of hormesis in skeletal muscle.

Historically, the perception that exercise-induced oxidative stress and inflammation cause muscle fatigue and damage has provoked widespread interest in countermeasures

such as antioxidant supplements, NSAIDs, and cryotherapy (31, 236). However, advances in our understanding of the role of RONS and inflammatory mediators in muscle adaptations to exercise have generated debate about whether these strategies are actually beneficial—at least in young healthy people (74, 162, 190). Antioxidant supplements and NSAIDs may help to preserve or enhance muscle adaptations to exercise in older individuals with impaired antioxidant defense systems or chronic low-grade inflammation (120, 228). By contrast, in young people these interventions can attenuate exercise-induced increases in insulin sensitivity (177) and muscle protein synthesis (229). The advantages or disadvantages of these interventions may therefore vary between different exercising populations. At the other end of the hormesis continuum, interest has also emerged in the potential benefits of applying stress to skeletal muscle before, during, or after exercise to stimulate greater adaptation. This stress can be applied by restricting carbohydrate intake, occluding local blood supply using low-intensity isometric or eccentric contractions (mechanical 'preloading'), or passively heating muscle.

Considering the increasing attention on strategies to enhance exercise performance and assist recovery, it is timely to debate the scientific rationale for using interventions such as cryotherapy, antioxidant supplements, NSAIDs, mechanical preloading, dietary carbohydrate restriction, heat stress, and blood flow restriction to modulate adaptations to exercise. The purpose of this review is to combine, integrate, and apply knowledge about how these interventions influence skeletal muscle adaptations to exercise under the overarching concept of hormesis.

INTERVENTIONS THAT ENHANCE EXERCISE-INDUCED HORMESIS

Restricting Dietary Carbohydrate Intake

Modulating skeletal muscle glycogen content by restricting dietary carbohydrate intake between exercise sessions is a relatively recent strategy to enhance exercise-induced hormesis. Glycogen is an important substrate for oxidative phosphorylation in skeletal muscle, and low muscle glycogen content is a key determinant of muscle fatigue (11, 94, 205). Accordingly, maximizing muscle glycogen content by carbohydrate loading before exercise and delaying the rate at which glycogen content is depleted (by ingesting carbohydrate during exercise) are common practices for athletes (21). Recent studies have used various diet and/or exercise protocols to manipulate muscle glycogen content before exercise sessions to determine whether changes in glycogen availability influence adaptive responses [for review see (8, 69)]. There is growing evidence of beneficial effects on metabolic and mitochondrial adaptations when exercising with low compared with normal muscle glycogen content. This section briefly examines the putative mechanistic influence of low muscle glycogen content and any potential for biphasic responses that support the hormetic model of adaptation.

Training with low muscle glycogen content promotes metabolic adaptation. A primary concept within the paradigm of nutrient–training interactions in skeletal muscle is that substrate availability mediates the cellular response to contractile activity (32). However, such a paradigm oversimplifies the complexity of how substrate availability modulates adaptation. Hansen et al (65) first examined whether repeated bouts of exercise begun with low muscle glycogen content induces greater metabolic stress and disruption to homeostasis in skeletal muscle. They found that resting muscle glycogen content and citrate synthase activity were higher in subjects who started half of their training sessions with low

glycogen versus those who always started training with normal glycogen. They concluded that this was because glycogen depletion caused by the first session dictated that the second session began with reduced muscle glycogen content. Although differences in the distribution of the training stimulus may have influenced these findings, there seems little doubt that the key factor promoting the adaptive response was training 'low'.

The metabolic flexibility of healthy skeletal muscle permits shifts in substrate oxidation based on the availability of carbohydrates and fats [for review see (205)]. Consequently, imposing the need for greater use of fat as a fuel likely explains much of the augmented adaptation to exercise with low initial muscle glycogen content. The demand for ATP supply during prolonged moderate- to high-intensity exercise is likely to also increase the magnitude of the adaptive signal under low-glycogen conditions. In this regard, the adenosine monophosphate activated protein kinase (AMPK) may be a focal point for regulating the cellular response to exercise with low initial muscle glycogen content, given its role as an energy sensor (66, 67). AMPK contains a glycogen-binding domain on one of its three subunits that causes it to colocalize with glycogen (66, 67, 128). AMPK also regulates the activity of several signaling pathways including those that promote glucose transport, fatty acid uptake, and mitochondrial biogenesis (66). The few studies that have quantified AMPK phosphorylation or activity after exercise begun with low- compared with normal/high-glycogen content have shown that the greater AMPK response in skeletal muscle following exercise is associated with lower preexercise glycogen content (242, 249).

Several other putative mediators of skeletal muscle adaptations to endurance exercise are enhanced after exercise with low initial muscle glycogen content. The phosphorylation status and mRNA abundance of important regulators of mitochondrial biogenesis (e.g.,

tumor suppressor p53 and peroxisome proliferator-activated receptor coactivator [PGC-1α]) are more responsive to exercise with low compared with high initial muscle glycogen (9, 172). Similarly, mitochondrial enzyme activity increases after extended training periods during which exercise is repeatedly begun with low muscle glycogen content (65, 140, 250). Exercising with an initially low glycogen content also induces favorable metabolic responses, including greater oxidation of triacylglycerol and net uptake of glucose and fatty acids into skeletal muscle (75, 242, 250). Peroxisome proliferator-activated receptor δ expression increases in skeletal muscle after acute and chronic exercise (161), and likely plays an important function in alterations in muscle substrate metabolism following exercise training (17). Collectively, these findings suggest that manipulating carbohydrate availability before and/or during exercise stimulates several of the molecular and metabolic responses that promote adaptations to training.

Adverse responses to low glycogen content. Low glycogen availability limits its use for oxidative phosphorylation and may impair excitation–contraction coupling in muscle during exercise. Specifically, the reduction in Ca^{2+} release from the sarcoplasmic reticulum (SR) that accompanies muscle fatigue is associated with depletion of intramyofibrillar glycogen content (144, 256). In support of this *in situ* evidence, exercise studies have shown that depletion of muscle glycogen decreases Ca^{2+} release from the SR (50, 255). Importantly, SR Ca^{2+} release remains suppressed when carbohydrate intake is restricted in the early (4 h) postexercise recovery period. By contrast, resynthesis of muscle glycogen returns SR Ca^{2+} release rates to the preexercise levels (50). Together with the potential to promote shifts toward greater fat oxidation and inferior rates of carbohydrate oxidation, these responses could explain, at least in part, why acute exercise intensity is lower and endurance

177 performance following chronic training does not improve when using the 'train low'
178 paradigm (75, 140, 250).

179 The increase in metabolic stress in skeletal muscle during exercise starting with low
180 glycogen content may also modulate protein turnover. In principle, higher AMPK activity
181 (resulting from low muscle glycogen content) could attenuate muscle protein synthesis by
182 inhibiting translation/elongation. Increased metabolic stress associated with low muscle
183 glycogen content may also exacerbate protein degradation (66, 72). Camera et al (23)
184 demonstrated that starting a bout of resistance exercise with low muscle glycogen content
185 neither promoted nor inhibited the myofibrillar protein synthesis. However, others have
186 reported that starting exercise with low muscle glycogen content increases the rates of
187 leucine oxidation and muscle protein degradation (13, 72). More research is needed to
188 determine the effects of training with low muscle glycogen content on protein turnover—
189 particularly during recovery between training sessions. Nevertheless, it is possible that
190 exercise starting with low compared with high muscle glycogen content may increase
191 muscle protein degradation.

192 Given the potential for conflicting beneficial and detrimental effects of training starting
193 with suboptimal glycogen content on skeletal muscle adaptations, a key question is: how
194 low should one go? If a biphasic response is dose dependent, one challenge is to titrate the
195 threshold for muscle glycogen content that might enhance the metabolic adaptations
196 without causing complications associated with fatigue or changes in the net protein balance
197 (Table 1). Perhaps the more pertinent question is not 'how low', but for 'how long' or 'how
198 often'. Although acute restriction of dietary carbohydrate provides a positive stimulus for
199 metabolic adaptation, repeated depletion or long-term reduction in muscle glycogen

content may lead to overtraining (4). Therefore, the benefits of restricting carbohydrate during exercise or training with low initial muscle glycogen content must be balanced against the risk of fatigue.

Blood Flow-Restricted Exercise

In addition to nutritional interventions, it is also possible to enhance exercise-induced hormesis through physical interventions. One such example is applying a pressure cuff to the proximal regions of a limb during exercise. This practice first originated in Japan and was initially termed 'Kaatsu' training, which means 'adding pressure' (187). The first research published in English was a study by Shinohara et al (200), in which the combination of moderate resistance (40% of maximum voluntary contraction) and tourniquet ischemia resulted in a significant increase in strength (in contrast to no change in strength in the leg that exercised without ischemia). This training method is now more frequently referred to as 'blood flow-restricted exercise' (108). The basic physiological premise behind blood flow-restricted exercise is that it reduces blood flow and occludes the venous return from the limb (blood pooling). This combination of stimuli increases tissue hypoxia and the accumulation of metabolites, and thereby increases muscular stress during low-load resistance exercise (209-211). Blood flow-restricted exercise induces muscle hypertrophy and increases in muscle strength in the same range as traditional heavy-load strength training. Importantly, blood flow-restricted exercise induces effects that are absent (or minor) when low-load exercise is performed without blood flow restriction (108, 114).

Blood flow restriction results in several local and systemic responses that might contribute to the enhanced hypertrophic stimulus when combined with low-load resistance exercise [20–30% of 1 repetition maximum (RM)] (113, 240). In addition to metabolite accumulation, the suggested mechanisms include increased recruitment of motor units (rapid development of fatigue) (240), greater growth hormone secretion (215) and oxidative stress (240), and muscle swelling (blood pooling) (110). Some of the mechanisms are directly related, because metabolic accumulation causes rapid onset of fatigue (which increases motor unit recruitment) and increases growth hormone secretion (215, 240). Because it is difficult to separate these mechanisms, it remains unknown which of these factors are most important. Nevertheless, combining blood flow restriction with low-load resistance exercise increases the rate of muscle protein synthesis by activating similar pathways to those activated after heavy-load strength training (e.g., mammalian target of rapamycin [mTOR] signaling and MAPKs) (45, 47, 60, 239). Furthermore, low-load blood flow-restricted exercise seems to induce a rapid and marked activation of satellite cells (239). Interestingly, this satellite cell activation appears to exceed that which occurs after traditional heavy-load strength training (145). Satellite cell activation induced by blood flow-restricted exercise is accompanied by an increase in the number of myonuclei, which may explain some of the muscle hypertrophy in response to blood flow-restricted exercise (18). The 30–40% increase in cross-sectional area of both type I and II fibers after only seven sessions of low-load, blood flow-restricted exercise supports the hypertrophic potential of this method (145). Others have also reported rapid hypertrophy in response to high-frequency (2×/day), low-load, blood flow-restricted exercise over 1–3 weeks (1, 3).

High-frequency, low-load blood flow-restricted exercise is generally a safe and effective training regimen because the low load induces less mechanical stress on muscle fibers than heavy-load strength training. In addition to the benefits described above, some studies also report no (or only minor) muscle damage and fast recovery after low-load, blood flow-restricted exercise (107, 112). However, the ischemia induced by blood flow restriction might cause some muscle damage and prolonged recovery if certain thresholds are passed. There are isolated reports of severe muscle damage resulting in rhabdomyolysis following blood flow-restricted exercise (82). Sarcolemmal and myofibrillar disruption and slow recovery of muscle function have also been reported after blood flow-restricted exercise in other studies (33, 241). These contrasting findings probably reflect differences in the training status of the study participants, degree of exhaustion, cuff pressure and size, and exercise intensity/volume.

Signs of damage, such as sarcolemmal disruption, high blood creatine kinase [CK] activity, and long-lasting fatigue, and rhabdomyolysis have been reported after the first session of low-load blood flow-restricted exercise (33, 82, 241), but rapid adaptation thereafter is likely. Performing a fixed number of repetitions per set (e.g., 15–15–15 or 30–15–15–15) causes little or no muscle damage (2, 111), but performing each set to failure causes more severe damage (33, 82, 241). The size of the cuff and the occlusion pressure can vary greatly. It can also be difficult to control arterial blood flow and venous return accurately (109). Collectively, these factors make it difficult to determine the optimal guidelines for blood flow restriction in combination with low-load resistance exercise.

Although the stress on the exercising muscle during low-load blood flow-restricted exercise is not well described, some interesting observations have been reported. In a

volume-matched protocol, blood flow-restricted exercise increased the acute expression of heat shock proteins (HSPs) in myofibrillar structures (33). Accumulation of small HSPs in myofibrillar structures was more abundant in type I fibers, indicating that low-load, blood flow-restricted exercise stresses type I fibers more than type II fibers, which contrasts with heavy-load strength training (43). This finding suggests that the combination of low-load resistance exercise and blood flow restriction preferentially stresses type I fibers. Provided that the stress remains within the optimal range, over the long term, such exercise also increases the hypertrophy of type I fibers. Importantly, in accordance with the hormesis theory, the dose is essential because excessive pressure and/or exercise volume/intensity may cause severe muscle damage, especially at the initiation of blood flow-restricted exercise.

In summary, applying a pressure cuff to restrict blood flow to an exercising limb—and thereby blocking venous return—increases the stress to the skeletal muscle during exercise. Blood flow restriction augments the effect of low-load resistance exercise on muscle hypertrophy. An important theme that arises from our evaluation is that blood flow restriction seems to shift muscular stress toward a more optimal range than that achieved with low-load exercise performed in isolation. However, the large variation in the application of blood flow restriction and exercise protocols makes it difficult to suggest an optimal protocol for low-load blood flow-restricted exercise at the present time. Acute blood flow restriction during exercise induces metabolic/hypoxic stress that ultimately leads to muscle hypertrophy. However, if used on a regular basis without sufficient recovery, blood flow-restricted exercise could induce a chronic cycle of muscle degradation and repair, which may impede rather than improve adaptations to training.

289

290 *Application of Heat to Muscle*

291 Applying heat to muscle is another physical intervention that may enhance exercise-
292 induced hormesis. Historically, heat has been used to treat severe muscle injuries (104),
293 although it may also improve recovery from less severe exercise-induced muscle damage.
294 The fundamental benefit of using heat in the management of muscle injuries involves an
295 increase in local blood flow (191, 245), which likely serves to improve the supply of oxygen
296 and nutrients to assist tissue repair (52). The alternative concept of using heat to
297 'precondition' cells and tissues against other forms of stress was recognized around 20 years
298 ago. It was termed 'cross-tolerance' (248), and is a classic example of hormesis. It has
299 stimulated interest in the potential for heat preconditioning to protect myocardial tissue
300 against infarction (121) and skeletal muscle against atrophy (142). An increasing number of
301 studies have investigated the effects of heat application before or after various forms of
302 muscle injury on muscle regeneration and the associated mechanisms (Table 2).

303 *Heat preconditioning.* There is convincing evidence that heat stress assists recovery from
304 muscle injury. Application of heat (41°C) before *in vitro* muscle contraction augments
305 protein synthesis and expression of HSP72 in muscle cells (55, 247). In rats, heat
306 preconditioning 12–48 h before muscle injury increases muscle fiber cross-sectional area
307 and number of centrally nucleated fibers (96). This form of treatment also minimizes fiber
308 degeneration (199) and mitochondrial damage (48) after injury, and assists in maintaining
309 muscle mass during reloading after immobilization in rats (199).

Various mechanisms have been identified to explain these effects including: (i) an increase in phosphocreatine content, which is associated with less necrosis (48, 181); (ii) maintenance of reactive oxygen species-scavenging activity (199); (iii) increased expression of myosin heavy chain protein and HSPs (193, 223); and (iv) more $Pax7^{+}$ satellite cells (96) in regenerating muscle. Heat preconditioning also reduces oxidative damage to muscle protein (193) and infiltration of mononuclear inflammatory cells (96, 199, 223) after muscle injury in rats. In addition to these studies on muscle injury, heat preconditioning increases the activity of PGC-1α and AMPK in C2C12 myotubes (84) and prevents muscle atrophy in response to immobilization (192) and hindlimb unloading in rats (142).

Research on the effects of heat preconditioning on recovery from exercise-induced muscle damage in humans has produced more variable findings. Some work indicates that heat stress before eccentric exercise can reduce muscle fatigue (77), promote faster recovery of strength and range of motion, and alleviate muscle soreness (149, 183). Heat preconditioning also increases the activation of Akt, mTOR, ribosomal protein S6, and eukaryotic translation initiation factor 4E-binding protein 1 (EIF4E-BP1) after resistance exercise (90). In contrast with these studies, others have reported no benefits of heat preconditioning on the recovery of strength, range of motion, edema, or soreness after eccentric exercise (86, 151).

Heat stress after muscle injury/exercise. Various animal studies have reported that applying heat after muscle injury increases muscle fiber cross-sectional area and number of centrally nucleated fibers (68, 71, 96, 154, 216). Consistent with the effects of heat preconditioning, these benefits of therapeutic heat treatment are conferred by upregulation of HSPs in muscle (71, 154). Heat application after muscle injury in rats also induces more rapid

macrophage infiltration (216); expression of IGF-1 (216), MyoD, and myogenin (68), calcineurin (154); and activity of $Pax7^+$, $MyoD^+$, and M-$cadherin^+$ satellite cells (96, 154, 216). Conversely, applying heat to muscle following injury reduces myeloperoxidase activity, production of RONS, lipid peroxidation, and fibrosis in rats (25, 71, 216).

Relatively little is known about how applying heat to muscle after exercise influences acute recovery of muscle function. One study reported that, compared with passive recovery, hot water immersion (38°C for 14 min) after eccentric exercise improved the recovery of strength, but not that of muscle power, swelling, or soreness (231). The same group reported that hot water immersion did not help to maintain sprint or time trial performance over 5 days of high-intensity cycling (230).

No studies have investigated the effects of regular heat application on chronic muscle adaptations to training. However, evidence from a recent study on rats suggests some potential benefits of heat to enhance training adaptations. In this study, rats that were placed in a heat chamber at 41°C for 30 min immediately after treadmill running showed greater chronic increases in the activity of citrate synthase and 3-hydroxyacyl CoA dehydrogenase, and mitochondrial protein content in skeletal muscle after 3 weeks of training (5 days/week) (217).

The transcription factor heat shock factor-1 (HSF-1) and it downstream effectors, HSPs, are most likely central to the benefits of heat stress for healing of muscle injuries, as demonstrated in animal studies outline below. HSF-1 and HSPs may assist muscle regeneration by protecting muscle cells against oxidative damage, apoptosis, and ATP depletion (16, 87-89, 118). HSPs may also promote repair of muscle tissue by activating the signaling pathways involved in protein synthesis (e.g., Akt, p70S6 kinase, and ERK) (61) and

by regulating the activity of enzymes and transcription factors that can cause degeneration and/or atrophy of muscle fibers (38, 49, 105, 195). Importantly, without HSF-1 and HSP70, macrophage infiltration is delayed, and the expression of proinflammatory cytokines is dysregulated in regenerating muscle tissue (98, 148, 196). Heat stress may also increase muscle hypertrophy independently of HSPs by stimulating the expression of IGF-1, myogenin, and Pax7 (166). Increased expression of IGF-1 in response to heat stress likely complements the effects HSPs by orchestrating more efficient resolution of inflammation following muscle injury (160).

This review is the first summary and critical evaluation of the effects of applying heat to muscle with the goal of promoting repair and growth of muscle. Acute heat stress increases the activities of HSPs, satellite cells, PGC-1α, and AMPK, whereas it reduces oxidative damage in muscle after exercise/injury. Over the long term, these responses may augment training adaptations. Although the application of heat stress before or after muscle injury has shown promising results in muscle cell culture and animal studies, more work is required to establish whether these same benefits occur in humans.

Mechanical Preloading

A single bout of eccentric muscle contractions confers protection against subsequent bouts of muscle-damaging exercise. This response is referred to as the 'repeated-bout effect', and may last between 6 and 9 months (150). The repeated bout effect can also occur in the non-exercising contralateral limb, although the effect in the contralateral limb is smaller than that in the ipsilateral limb (73).

Recent interest has focused on trying to determine the minimum stimulus required to elicit protection against muscle damage, which is typically characterized by prolonged decreases (>1 d) in muscle function and delayed-onset muscle soreness (DOMS). Herein, we refer to this approach to strength training and conditioning as 'mechanical preloading'. Although this is a relatively new concept, it is a classic example of exercise-induced hormesis, whereby mild mechanical preloading of skeletal muscle induces positive adaptations. The first evidence for the benefits of mechanical preloading came from a study demonstrating that low-intensity isometric contractions (performed at 10% of maximal voluntary contraction strength) improved the recovery of strength by 50–60% and reduced peak muscle soreness by 30% after subsequent eccentric exercise performed 2 days later (101). These protective effects of mechanical pre-loading seem to last between 1 and 2 weeks (26).

Mode and intensity of contraction. The preloading effect does not appear to be specific to the type of muscle contraction. Preloading with as few as two maximum voluntary isometric contractions at a long muscle length (20° flexion) is sufficient to attenuate the loss of strength and range of motion, DOMS, and swelling after eccentric exercise performed 2 days later (27). As evidence of a dose response, 10 maximal voluntary isometric contractions at the same muscle length conferred even greater protective effects (27). The protective effect conferred by two maximal isometric contractions appears to last only a maximum of 1 week (28). Compared with low-intensity eccentric contractions (10% maximum strength), maximal isometric contractions performed at 20° flexion confer a greater degree of protection against subsequent muscle damage (30). However, the protective effect of maximal isometric contractions is less than that resulting from maximal eccentric

401 contractions (30). Four bouts of moderate-intensity eccentric exercise comprising eccentric
402 contractions at 40% of maximal voluntary isometric contraction, performed every 2 weeks,
403 confers a similar protective effect to one bout of maximal eccentric exercise (29). This
404 finding suggests that repeating submaximal eccentric exercise provides the same protection
405 as one bout of maximal eccentric exercise against the subsequent maximal eccentric
406 exercise. It remains to be determined whether regular lighter intensity eccentric
407 contractions (e.g., 10%) or maximal isometric contractions at a long muscle length increase
408 long-term muscle adaptations.

409 Integration of the findings of the small number of studies in this area shows that a few
410 eccentric contractions at low intensity or a few maximal isometric contractions at long
411 muscle length confer significant protection against subsequent muscle damage. In addition
412 to contracting muscles, this effect most likely also occurs in non-exercising muscles of the
413 contralateral limb. The mechanisms underpinning the effects of mechanical preloading on
414 muscle adaptation are currently unknown. Adaptation to maximal eccentric contractions
415 has been attributed to various factors, including neural changes (e.g., increased motor unit
416 recruitment/synchronization), remodeling of connective tissue, removal of weak fibers, and
417 longitudinal addition of sarcomeres (131). Light-intensity eccentric contractions and
418 isometric contractions do not cause any loss of strength or range of motion, muscle
419 swelling, or DOMS (27, 101). Without causing frank muscle damage, these types of
420 contractions may precondition skeletal muscle through other mechanisms. Such
421 mechanisms could include physical changes to the fascia and endomysium or metabolic
422 alterations in ATP availability, intracellular [Ca^{2+}], mitochondrial Ca^{2+} uptake, RONS signaling,

423 or proteolytic activity. Further research is warranted to examine these putative mechanisms
424 in greater detail.

425 Because acute muscle damage resulting from mechanical preloading is minimal, it seems
426 unlikely that long-term use of this form of preconditioning will increase the risk of
427 maladaptation to training. However, the protective effect of mechanical preloading may
428 diminish if it is used repeatedly because muscle probably adapts to such mechanical
429 stimulation. Consistent with this premise, any benefits of mechanical preloading are
430 probably relatively minor for resistance-trained individuals who regularly perform
431 submaximal eccentric contractions and maximal isometric contractions in their training
432 routines. Future studies in this area could investigate whether skeletal muscle
433 remodeling/hypertrophy is still induced effectively if no muscle damage is induced
434 throughout training.

435

436 **INTERVENTIONS THAT DAMPEN EXERCISE-INDUCED HORMESIS**

437 *Antioxidant Supplementation*

438 The notion of hormesis has been studied extensively in the context of oxidative stress
439 and its opposing roles in skeletal muscle pathologies. It has also been examined as a
440 potential stimulus for redox adaptations in skeletal muscle following endurance training. For
441 the purposes of this review, the term ‘oxidative stress’ is defined as an imbalance between
442 oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling
443 and control and/or molecular damage (171). Davies et al (34) were the first to report that
444 submaximal exercise to exhaustion increased the production of free radicals in rodent

skeletal muscle. Other more recent studies have also shown that exhaustive endurance exercise increases oxidative stress in rat skeletal muscle (10, 91, 235). Although these studies provide vital proof of principle, understanding precisely how RONS regulate skeletal muscle adaptations to endurance training is difficult—mainly because few training programs regularly push individuals to exhaustion. Nevertheless, moderate- to high-intensity endurance exercise (70–85% of maximal oxygen uptake) is sufficient to increase oxidative stress in rat skeletal muscle, as measured by changes in GSSG levels (237, 238, 254). Moderate-intensity endurance cycling exercise is also sufficient to increase lipid peroxidation, as measured by F_2-isoprostane content in skeletal muscle of humans (92). Bailey et al (7) provided the first direct evidence in humans that exercise in the form of maximal, single-leg knee extension increases intramuscular free radical accumulation.

Oxidative stress and mitochondrial biogenesis in skeletal muscle. Redox-sensitive kinases activated during muscle contraction include AMPK, activating transcription factor-2 (ATF-2), NFκB, and the MAP kinases p38 MAPK, JNK, and ERK (also called p44/42 MAPK) (53, 79, 185, 238). These kinases are all implicated in the regulation of mitochondrial biogenesis (83, 243)—at least partly through the transcriptional coactivator PGC-1α, which is a key regulator of mitochondrial biogenesis (173, 244). Although RONS were first proposed to regulate exercise-induced mitochondrial biogenesis over 30 years ago (34), it was Silveira et al who first published clear evidence linking RONS with the regulation of contraction-induced mitochondrial biogenesis in rat muscle cells (201). Importantly, this group demonstrated that antioxidants attenuated the increase in RONS production and PGC-1α mRNA expression (201). Hood et al (79) have since provided more direct evidence for the role of RONS (and antioxidants) in regulating the expression of AMPK and PGC-1α in skeletal

muscle cells. Other proteins such as upstream stimulatory factor 1 also play an important role in regulating PGC-1α activity in skeletal muscle (80).

Antioxidants and mitochondrial biogenesis. Research on the effects of antioxidants on mitochondrial biogenesis has used vitamins C and E (alone or in combination), coenzyme Q10, *N*-acetylcysteine, β-carotene and α-lipoic acid in rats (54, 70, 208, 234) and humans (157, 163, 177, 251). Because of the large number of individual antioxidant supplements, a comprehensive examination of each antioxidant is beyond the scope of the current review (for review, see (120). This review is limited to evaluation of hormesis specifically in relation to vitamins C and E because they are two of the most common antioxidant supplements used alone or in combination by the general population (180) and in research (54, 70, 157, 177, 208, 234, 251). Given the role of RONS in stimulating mitochondrial biogenesis in skeletal muscle (79, 201), many studies have investigated whether antioxidant supplements prevent adaptations to endurance training. Some training studies have found that vitamin C and/or vitamin E attenuates markers of mitochondrial biogenesis in muscle after training in rats (54, 234) and humans (157, 177). By contrast, other studies have found no significant effects of antioxidant supplements on markers of mitochondrial biogenesis (70, 208, 251, 253).

Despite this evidence for a reduction in cellular adaptations to endurance training with antioxidants (54, 157, 177, 234), no research has reported any change in maximum oxygen uptake or exercise performance—at least in humans (157, 178, 251). Animal studies have demonstrated that vitamin C supplementation reduces the improvements in exercise performance after 6 weeks of exercise training (54, 126). Differences in the metabolism of

490 vitamin C in skeletal muscle between humans and rats may partially account for these
491 differences.

492 Despite strong evidence that endurance exercise increases oxidative stress in human
493 skeletal muscle (7, 92, 254), it remains uncertain whether vitamin C and/or E
494 supplementation inhibits oxidative stress in human skeletal muscle during exercise. One
495 reason for this uncertainty is the lack of suitable markers of RONS production and oxidative
496 stress in skeletal muscle during exercise. Some studies have used plasma or blood to assess
497 oxidative stress (70, 157). However, this is problematic because the degree of systemic
498 oxidative stress in plasma/blood may not reflect the extent of local oxidative stress in
499 skeletal muscle (235). Furthermore, other markers of oxidative stress (e.g., thiobarbituric
500 acid reactive substances (TBARS) or malondialdehyde) may not be specific or sensitive to
501 antioxidant supplementation (182, 252).

502 In addition to discrepancies between the effects of antioxidants in animals compared
503 with humans, there is also some disparity between the acute and chronic effects of
504 antioxidants. For example, several acute exercise studies show that inhibiting RONS derived
505 from xanthine oxidase with the xanthine oxidase inhibitor, allopurinol, inhibits the exercise-
506 induced phosphorylation of redox-sensitive kinases such as p38 MAPK and ERK, which
507 regulate mitochondrial biogenesis in rats (53, 91, 238). However, long-term treatment with
508 allopurinol does not prevent the increases in skeletal muscle mitochondrial proteins or
509 antioxidant enzymes following endurance training in rats (238). One possible reason for this
510 disparity is that stimuli other than RONS, such as cytosolic Ca^{2+} (130, 155), AMP (130), and
511 possibly NAD (51) also regulate mitochondrial biogenesis in skeletal muscle. Thus, although
512 antioxidant supplements can inhibit RONS production in skeletal muscle, this may not

513 always attenuate mitochondrial biogenesis probably because of redundancies within these
514 pathways.

515 *Antioxidants and skeletal muscle hypertrophy.* There is substantial evidence linking oxidative
516 stress with muscle atrophy [for review see (170)]. Emerging evidence also implicates
517 oxidative stress in the regulation of skeletal muscle hypertrophy. A high daily oral dose of
518 vitamin C attenuates skeletal muscle hypertrophy and oxidative stress normally observed
519 following mechanical overload of the plantaris (119). Recent findings in rodents
520 demonstrate that the highly reactive oxidant, peroxynitrite regulates skeletal muscle
521 hypertrophy induced by overload (81). Peroxynitrite appears to operate by stimulating the
522 release of intracellular Ca^{2+}, which then activates mTOR to increase protein synthesis (119).

523 The few human studies to investigate the adaptations to resistance training combined
524 with antioxidant supplementation have reported variable findings. Two studies showed no
525 effect of vitamin C and E supplementation on improvements in skeletal muscle strength or
526 performance (14, 220). However, these studies used resistance training protocols that did
527 not induce skeletal muscle hypertrophy (14) or did not measure changes in lean muscle
528 mass (220). Paulsen et al (159) recently found that supplementation with vitamins C and E
529 attenuated the activities of several kinases involved in hypertrophy signaling, such as p70S6
530 kinase and the redox-sensitive kinases p38 MAPK and ERK 1/2 in skeletal muscle after 10
531 weeks of resistance training. In addition, supplementation attenuated bicep curl strength
532 following 10 weeks of training. By contrast, supplementation did not alter protein synthesis
533 or muscle hypertrophy following training (159). Thus, some evidence supports blunting of
534 the cell signaling pathways with antioxidant supplementation following resistance exercise,
535 although the effects on functional outcomes remain equivocal. More studies are required to

examine whether RONS regulate hypertrophy following resistance training in human skeletal muscle and whether antioxidant supplementation influences these adaptations to resistance exercise.

In summary, oxidative stress plays an important role in regulating the mitochondrial content and perhaps contractile protein content of skeletal muscle. Some evidence shows that supplementation with vitamins C and E can block acute increases in signaling pathways that control mitochondrial biogenesis and hypertrophy. However, these acute responses do not consistently translate to less mitochondrial biogenesis or muscle hypertrophy following chronic exercise training because of the apparent redundancy in skeletal muscle. That is, exercise training (either endurance or resistance) may induce mitochondrial biogenesis and hypertrophy despite elevated concentrations of RONS-scavenging antioxidants. The weight of current evidence suggests that vitamin C and E supplementation may dampen exercise-induced hormesis—at least at the cellular level. However, it remains uncertain whether these responses influence exercise performance in the long term. Importantly, antioxidant compounds have widely divergent properties, and this discussion of a specific class of agents does not rule out the effects of other components on RONS activity/regulation, nor a role for RONS in exercise-induced adaptation. The requirement for and efficacy of antioxidant supplements may vary with age and health status. There are conflicting and unresolved issues surrounding the influence of antioxidant supplementation on adaptations to training that require further investigation.

NSAIDs

Similar to antioxidants, NSAIDs represent another pharmacological intervention that may attenuate exercise-induced hormesis. NSAIDs are inhibitors of the cyclooxygenase (COX) pathway that converts free arachidonic acid to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (42, 232). PGs are autocrine/paracrine lipid mediators that propagate the inflammatory response to tissue injury by increasing blood flow, vascular permeability, and leukocyte chemotaxis (35). COX has two major isoforms. COX-1 is constitutively expressed, and COX-2 expression is generally low but is highly inducible in response to injurious stimuli (57, 139). Classical NSAIDs inhibit both COX-1 and COX-2 to varying degrees (36, 202). Undesirable side effects associated with disruption of homeostatic COX-1 activity have led to the development COX-2-specific inhibitors (coxibs) for treating pain and inflammation. During postexercise recovery, the activities of COX-1 and COX-2 (24) and concentrations of PGs (20, 93, 225, 227) increase transiently in skeletal muscle. Plasma PG concentrations also increase after exercise (39, 123, 218). These responses point to important roles for the COX/PG pathway in exercise adaptation. On the other hand, chronically elevated PG concentrations are associated with—and may contribute directly to—muscle wasting in states of chronic inflammation (97).

Effect of NSAIDs on acute muscle responses to exercise. Classical NSAIDs (e.g., ibuprofen and indomethacin) administered at over-the-counter doses effectively block the acute exercise-induced increase in PG concentration in muscle (20, 135, 227) and plasma (123). Although not considered a classical NSAID, acetaminophen also appears to inhibit COX activity in muscle (227). Many studies have investigated the effect of NSAIDs on symptoms of exercise-induced muscle damage, although the literature on the efficacy of NSAIDs for reducing muscle soreness and/or improving exercise recovery is contradictory. Given that NSAIDs are

581 anti-inflammatory, it is surprising that studies to date have failed to observe any effect of
582 NSAIDs on systemic (95, 167, 222) or intramuscular (158) leukocyte responses to exercise
583 stress. Paradoxically, short-term NSAID treatment appears to increase plasma cytokine
584 concentrations (e.g., IL-6 and monocyte chemotactic protein-1) (41, 59, 138, 146) and
585 muscle COX-2 gene expression (19, 138) after exercise.

586 Together with a lack of a clear benefit of NSAIDs in reducing exercise-induced pain
587 and/or the acute inflammatory response in humans, various studies have shown potential
588 negative effects of NSAIDs in muscle after exercise. Oral ingestion of the nonselective
589 NSAIDs ibuprofen or acetaminophen blunts the increase in muscle protein synthesis during
590 postexercise recovery in young men (229). However, this effect was not replicated in a study
591 of patients with knee osteoarthritis who received ibuprofen (165). Another nonselective
592 NSAID (indomethacin) blocked the muscle satellite cell response to a 36 km run (117) and
593 maximal eccentric exercise (137) but did not alter muscle protein synthesis (138). Studies
594 have shown that COX-2-selective inhibitors do not influence muscle protein synthesis (19) or
595 satellite cell responses to exercise (158), suggesting that COX-1 rather than COX-2 may be
596 the primary isoform involved in human muscle responses to exercise.

597 The underlying mechanisms by which NSAIDs influence muscle adaptive responses to
598 exercise remain unclear, but several recent studies have provided useful insights. Impaired
599 satellite cell proliferation following maximal eccentric exercise with local indomethacin
600 infusion (135) did not alter the expression of growth factors and extracellular matrix-related
601 genes (138) or HSP (136) in muscle. Oral ibuprofen treatment blocked the normal increase
602 in serum PG concentration during early postexercise recovery (0–3 h) (123), and suppressed
603 phosphorylation of components of the ERK and mTOR signaling pathways in muscle (122).

These data provide the first evidence that PGs contribute to contraction-induced signaling in human muscle and provide mechanistic support for a potentially detrimental effect of oral nonselective NSAIDs (122, 125). Interestingly, mass spectrometry profiling of serum samples collected throughout exercise recovery revealed suppression of both early proinflammatory and later anti-inflammatory/proresolving lipid mediator circuits in subjects receiving ibuprofen (123). Thus, NSAIDs may interfere with exercise recovery indirectly by delaying or preventing timely resolution of the inflammatory response (123, 233).

Chronic effects of NSAIDs on muscle exercise adaptation. Although nonselective NSAIDs may attenuate acute responses to exercise in humans (122, 123, 137, 138, 227, 229), it remains unclear whether these responses influence long-term adaptations to exercise. Oral ibuprofen treatment (400 mg/day) did not influence muscle hypertrophy or strength following 6 weeks of resistance training of the elbow flexors in young healthy men (99). However, this dose of ibuprofen was only one-third that used in acute exercise studies (122, 123, 227, 229). By contrast, animal studies clearly show a deleterious effect of NSAID treatment on long-term muscle regeneration and hypertrophy, and specifically implicate the COX-2 isoform in this response (100, 124, 152, 198).

In older adult subjects, gains in skeletal muscle size and strength following 12 weeks of resistance training were greater in response to treatment with ibuprofen (1,200 mg/day) or acetaminophen (4 g/day) compared with a placebo treatment (224). Another study also revealed that ibuprofen augmented training-induced gains in muscle strength in elderly subjects but did not influence muscle mass and tended to reduce satellite cell numbers in muscle (164). By contrast, a lower dose of acetaminophen (1,000 mg/day) did not alter fat-free-mass or muscle strength in older men after a period of resistance exercise training (85).

One mechanism through which NSAIDs may exert positive effects on muscle involves a reduction in chronic low-grade inflammation that occurs with aging, thereby blocking the pathway to muscle atrophy. NSAID treatment counteracts skeletal muscle wasting in animal models of chronic inflammatory disease including cancer cachexia (129, 202, 207), arthritis (56), and aging (176). Consistent with this hypothesis, older adults who received ibuprofen throughout 12 weeks of resistance training showed a chronic reduction in the expression of cytokine genes (e.g., IL-6, IL-10) and muscle ring finger 1 (MuRF-1) (226).

In summary, the COX/PG pathway appears to play an important role in acute exercise recovery, and NSAIDs inhibit the seemingly beneficial acute muscle adaptive responses to exercise (e.g., satellite cell proliferation and muscle protein synthesis). On the other hand, chronic activation of the COX/PG pathway may exert negative effects on muscle mass, and NSAID treatment may provide an effect countermeasure against such effects. In this review, we have highlighted an apparent discrepancy between the opposing effects of NSAIDs in different settings (e.g., acute versus chronic, young versus old subjects). The balance between PG species with differing bioactivity (e.g. $PGF_{2\alpha}$ versus PGE_2) (228) or differences in the underlying nature of the inflammatory response (acute self-resolving versus chronic nonresolving) (97, 122) may be important factors that influence the pharmacological actions of NSAIDs.

Cryotherapy

Cryotherapy in the form of ice massage and application of crushed ice has long been a common treatment for soft tissue injuries (132). More recently, other forms of cryotherapy

649 such as cold water/ice baths and brief exposure to extreme cold air (–20 to –110°C) in
650 custom-made cryotherapy chambers have gained popularity as strategies to recover from
651 exercise. Traditionally, the physiological basis for using cryotherapy has been to relieve pain,
652 reduce tissue metabolism, and modify vascular responses to minimize edema (213). Acute
653 responses to primary muscle injury (e.g., necrosis and inflammation) can result in
654 'secondary injury' to healthy cells not damaged through the initial trauma (134). By reducing
655 the metabolic rate of tissues within and around the injury site, cryotherapy may protect the
656 healthy bystander cells from the ischemic environment in the immediate period after injury,
657 thereby reducing the risk of secondary cell injury or death (12). Some evidence from animal
658 studies support this notion (133, 134, 156, 186). However, the effects of cryotherapy on
659 muscle inflammation in humans are currently unknown.

660 *Effects of cryotherapy on inflammation and oxidative stress.* Studies have focused on how
661 icing influences inflammation and oxidative stress in muscle following injury (Table 3).
662 Superfusing rats with cold saline (3–8°C) for 10 min to 6 h after muscle contusion injury
663 significantly reduced leukocyte rolling and adhesion to venules within damaged muscle for
664 up to 1 day after injury (102, 188, 189). These effects may be mediated by downregulation
665 of adhesion molecules on the surface of vessels and leukocytes in response to hypothermia
666 (63, 78). Immunohistochemical analysis of muscle tissue revealed that this cryotherapy
667 treatment decreased the number of neutrophils in muscle 1 day after injury (188, 189). In
668 support of these findings, others have observed that icing after muscle strain injury in rats
669 substantially reduced neutrophil activation in muscle, as indicated by lower
670 myeloperoxidase activity 1 day after injury (25). Icing also restricted the production of RONS
671 and lipid peroxidation at 1, 5, 10 and 15 days after injury in rats (25). Icing preserves the

activity of Na^{+}-K^{+}-ATPase and Ca^{2+}-ATPase enzymes and mitochondrial membrane permeability, and it reduces mitochondrial swelling in muscle 1 day after contusion injury in rats (174). Because none of these studies assessed muscle regeneration in the weeks following injury, it is difficult to establish whether restricting neutrophil invasion and activation through cryotherapy results in better healing of muscle injuries. In principle, a decrease in neutrophil infiltration into muscle as a result of icing is potentially beneficial because activated neutrophils can damage skeletal muscle fibers (143, 168).

Effects of cryotherapy on muscle regeneration. Other studies in rats have shown that icing causes greater fibrosis and impairs muscle regeneration after muscle contusion and crush injuries. These effects are evident as early as 2 days after injury (76) and persist for up to 4 weeks (214). The potential mechanisms responsible for these effects include delayed macrophage infiltration and mRNA expression of transforming growth factor-β1 and IGF-1 in muscle, together with a delay in (or absence of) satellite cell activation (76, 214). Impaired muscle regeneration in response to icing may be attributed to the following sequence of events. By restricting neutrophil infiltration, icing may slow the rate of phagocytosis of necrotic muscle tissue in the first few hours after injury (219). Persistent necrosis may then delay the entry of macrophages into muscle tissue in the first few days after injury (58). Finally, by delaying macrophage infiltration, icing may reduce the capacity of these cells to (a) produce essential growth factors and chemotactic agents (64, 115, 116, 212), and (b) stimulate satellite cells to proliferate and differentiate (6, 221). The limited evidence that is currently available therefore suggests that cryotherapy is detrimental for muscle regeneration following injury.

694 *Effects of cryotherapy on training adaptations.* In addition to this research on acute muscle
695 injury, a smaller body of research has investigated the effects of regular cryotherapy on
696 muscle adaptations to exercise training. An early study demonstrated that, in rats regularly
697 immersed in cold water (4°C) for 5 min after exercise bouts, greater ultrastructural damage
698 to myofibrils was evident after 5 weeks of exhaustive running and 7 weeks of moderate
699 running (46). Fu et al proposed that, by masking pain, cold water immersion allowed the
700 rats to exercise at higher intensities the next day, which unexpectedly resulted in greater
701 muscle damage (46). Subsequently, several human studies have also reported that regular
702 cold water immersion after exercise attenuates muscle adaptations to training (44, 153,
703 179, 246). The mechanisms by which regular cold water immersion dampened training
704 adaptations in these studies are unknown. Hypothetically, a decrease in muscle blood flow
705 in response to cold water immersion might reduce angiogenesis and protein synthesis in
706 muscle during recovery from exercise. In turn, these responses may result in smaller gains in
707 muscular endurance and strength.

708 This review is the first critical evaluation of the short- and long-term effects of various
709 forms of cryotherapy on cellular responses in skeletal muscle. We have also outlined in
710 detail the putative mechanisms by which cryotherapy influences muscle repair and growth.
711 When applied acutely after exercise or muscle injury, cryotherapy may help to reduce
712 muscle soreness and minimize secondary tissue damage. However, by attenuating some key
713 inflammatory reactions (e.g., macrophage infiltration) in skeletal muscle, cryotherapy may
714 also block the production and release of important growth factors and the activity of
715 satellite cells, which are important mediators of muscle repair and adaptation. Therefore,

716 although cryotherapy offers some short-term benefits, these are possibly outweighed by
717 long-term detrimental effects.

718

719 **PERSPECTIVES AND FUTURE DIRECTIONS**

720 This is the first commentary to combine, summarize, and evaluate the efficacy of
721 various strategies to modulate exercise-induced hormesis. Some of these strategies (e.g.,
722 antioxidant supplementation, treatment with NSAIDs, restriction of dietary carbohydrate
723 intake) have been the subject of scientific scrutiny and debate. By contrast, other strategies
724 such as cryotherapy, blood flow restriction, heat stress, and mechanical preloading have
725 received less critical attention. In this review, we have detailed the conceptual frameworks
726 for the use of such strategies, have integrated these details with the current knowledge
727 about the basic biochemical and molecular machinery that regulate muscle adaptations to
728 exercise, and have applied this information to assess the advantages and disadvantages of
729 each strategy for modulating exercise-induced hormesis.

730 Table 4 summarizes the mechanisms of action of treatments that modulate exercise-
731 induced hormesis and describes some of the short- and long-term outcomes of these
732 treatments. A key finding from this review is that there appears to be some dissociation
733 between the biochemical/molecular effects and functional/performance outcomes of some
734 of these treatments (e.g., antioxidants, NSAIDs, restriction of dietary carbohydrate).
735 Conceivably, other signaling pathways that are less responsive to these treatments (or not
736 yet defined) may operate independently in the regulation of training adaptations. This
737 redundancy may promote fine-tuning of adaptive responses to exercise training (40). Few of

738 the interventions described in this review have been adequately tested to determine if or
739 how they exert dose-dependent effects on muscle adaptation. If such dose-dependent
740 effects do occur, they are likely to be subject to highly complex regulatory mechanisms.

741 A common feature of hormesis is that exposure to one type of hormetic agent can
742 protect cells/organisms against more types of stress (127). This concept of 'cross tolerance'
743 may be applied to some of the interventions that we have discussed. Several of the
744 interventions influence common kinases, transcription factors, and proteins (see Table 4).
745 For example, AMPK, p38 MAPK, PGC-1α, and HSP expression increases in response to heat
746 stress, carbohydrate restriction, and blood flow restriction, whereas the expression of most
747 of these factors decreases following antioxidant supplementation. Similarly, macrophage
748 infiltration, IGF-1, and Pax7 expression increases in response to heat stress, whereas these
749 factors are either blocked or activated more slowly after cryotherapy. It remains to be
750 determined whether these interventions complement or negate each other and whether
751 such effects are strong enough to alter terminal adaptive processes such as mitochondrial
752 biogenesis, substrate metabolism, or muscle repair/growth.

753 Several important questions have emerged from this review that warrant further
754 investigation. A primary issue relates to the threshold (i.e., dose, period of exposure) that
755 defines whether oxidative stress and inflammation are beneficial for or harmful to muscle
756 adaptations to exercise. This threshold would be difficult to titrate because it most likely
757 depends on the basal state of oxidative stress and inflammation at the start of exercise. In
758 turn, this basal state may depend on periodization of training and recovery, together with
759 age, health status, and diet. In addition, it is unclear whether undertaking different
760 strategies simultaneously enhances or attenuates exercise-induced hormesis and which

761 combination of strategies might offer complementary or additive benefits. As highlighted in
762 our review, some interventions such as NSAIDs and antioxidants exert different effects in
763 young compared with older individuals and in trained compared with untrained individuals.
764 Finally, the efficacy of a given intervention may depend on the capacity to 'periodize' such
765 interventions during different phases of a training program. For example, during training to
766 promote muscle hypertrophy and strength, interventions such as cryotherapy and the use
767 of NSAIDs may dampen rather than enhance adaptation. However, during periods of regular
768 competition when recovery is a priority, these strategies may be appropriate to alleviate
769 muscle soreness and restrict secondary tissue injury.

770 In conclusion, exercise-induced adaptations in skeletal muscle are regulated through
771 interactions between various mechanical, metabolic, and physiological stressors and
772 complex cellular machinery. Undoubtedly, a large body of work is still required to provide
773 greater clarity on the appropriate uses and applications of strategies to modify skeletal
774 muscle phenotypes. Exercise-induced hormesis is an intriguing notion that awaits further
775 exploration. To adapt a phrase from a well-known bard, to intervene or not intervene: that
776 remains the question.

777

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1502 **Tables**

Table 1. Effects of glycogen concentration on physiological responses to exercise in human skeletal muscle.

Reference	Design	Δ%	Low glycogen	Findings
(242)	Acute	–82%	163 mmol·kg^{-1}·dw	↑AMPK activity
(9)	Acute	–75%	103 mmol·kg^{-1}·dw	↑p53 phosphorylation ↑Mitochondrial mRNA
(172)	Acute	–65%	166 mmol·kg^{-1}·dw	↑Mitochondrial mRNA
(13)	Acute	–47%	167 mmol·kg^{-1}·dw	↑Protein degradation
(72)	Acute	–30%	290 mmol·kg^{-1}·dw	↑Leucine oxidation ↓Net protein balance
(23)	Acute	–52%	180 mmol·kg^{-1}·dw	↔ Muscle protein synthesis
(255)	Acute	–69%	167 mmol·kg^{-1}·dw	↓SR Ca^{2+} release rate
(50)	Acute	–68%	245 mmol·kg^{-1}·dw	↓ SR Ca^{2+} release rate
(65)	Chronic	–68%	210 mmol·kg^{-1}	↑Mitochondrial enzyme activity
(250)	Chronic	–50%	250 µmol·g^{-1}·dw	↑Mitochondrial enzymes ↑Fat oxidation

dw, dry weight; SR, sarcoplasmic reticulum.

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Table 2. Summary of studies investigating the effects of heat stress on muscle regeneration.

Reference	Study type	Treatment	Assessment period	Outcome variables
(48)	Rats; ischemia	Hot water @ 42.5°C Duration: 20 min Timing: 12 h preinjury	1.5 h postinjury	Electron microscopy, PCr, ATP, HSP72
(199)	Rats; downhill running	Heat chamber at 42°C Duration: 60 min Timing: 48 h preinjury	1, 2, 3, and 7 d postinjury	ROS production and scavenging, HSP72, histology
(223)	Rats; downhill running	Hot water @ 43°C; Duration: 20 min Timing: 48 h preinjury	2 h and 2 d postinjury	Histology, Akt, p70S6K, ERK1/2, JNK, HSP72, HSP25, MHC
(96)	Rats; cardiotoxin injury	Heat chamber at 41°C Duration: 60 min Timing: 24 h preinjury or 0 h postinjury	1, 3, 7, 14, and 28 d postinjury	Muscle mass, central nucleated fibers, fiber CSA, HSP72, Pax7
(25)	Rats; acute strain injury	Infrared lamp Duration: 5 min Timing: 30 min and 2×/day postinjury	1, 5, 10, and 15 d postinjury	Lipid peroxidation, antioxidant enzymes myeloperoxidase
(154)	Rats; cardiotoxin injury	Hot water @ 42°C Duration: 30 min Timing: 48 h postinjury and then every second day	7 and 15 d postinjury	Fiber CSA, myonuclei, Pax7, M-Cadherin, MyoD, HSP72, calcineurin
(71)	Rats; tenotomy	Heat chamber @ 40.5–41°C Duration: 30 min Timing: 24 h preinjury; 1–6 d postinjury	7 d postinjury	Muscle mass, histology, fiber CSA, HSP72, collagen, TGF-β1, MMP-2, MMP-9, TIMP
(216)	Rats; acute crush injury	Hot pack @ 42°C Duration: 20 min Timing: 5 min postinjury	6 and 12 h; 1–7, 14, and 28 d postinjury	Central nucleated fibers Fiber CSA, macrophages TGF-β1, IGF-1, Pax7, collagen
(68)	Rats; acute crush injury	Hot pack @ 42°C; Duration: 20 min Timing: 5 min postinjury	12 h; 1–5, 7, 14, and 28 d postinjury	MyoD, myogenin, PCNA Pax7

(217)	Mice; acute treadmill running	Heat chamber @ 41°C Duration: 30 min Timing: Immediately postexercise	30 min postexercise	AMPK, ACC, p38 MAPK, CaMKII, Akt, mTOR p70S6K

Abbreviations: PCr, phosphocreatine; MHC, myosin heavy chain; PCNA, proliferating cells nuclear antigen; ROS, reactive oxygen species; CaMK, calmodulin-dependent protein kinase; CSA, cross-sectional area; Akt, protein kinase B; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase. See Figure 1 for details of other abbreviations.

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Table 3. Studies investigating the effects of cryotherapy on muscle regeneration.

Reference	Study type	Treatment	Assessment period	Outcome variables
(214)	Rat; acute crush injury	Topical icing Duration: 20 min duration Timing: 5 min postinjury	6 and 12 h; 1–7, 14, and 28 d postinjury	Central nucleated fibers Fiber CSA, macrophage , TGF-β1, IGF-1, Pax7, collagen
(25)	Rat; acute crush injury	Topical icing Duration: 5 min Timing: 30 min and 2×/d postinjury	1, 5, 10, and 15 d postinjury	Lipid peroxidation Antioxidant enzymes Myeloperoxidase
(174)	Rat; acute contusion injury	Topical icing Duration: 5 min Timing: Immediately and 6 h postinjury	1 d postinjury	Lipid peroxidation Antioxidant enzymes Myeloperoxidase Na^{+}-K^{+} ATPase, Ca^{2+} ATPase Lactate dehydrogenase
(76)	Rat; acute contusion injury	Topical icing Duration: 5 min; intermittently for 1 h Timing: Immediately postinjury or 24 h postinjury	1, 2, and 6 h; 1, 2, 5, and 7 d postinjury	Neutrophil infiltration Macrophage infiltration $Desmin^{+}$ myoblasts
(102)	Rat; acute contusion injury	Cold saline (3°C) infusion Duration: 10 min Timing: 5 min postinjury	15 min postinjury	Leukocyte rolling and adhesion
(189)	Rat; acute contusion injury	Cold saline (8°C) infusion Duration: 20 min Timing: ~20 min postinjury	1 h postinjury	Edema, microvascular perfusion, leukocyte rolling/adhesion Neutrophils and macrophages
(188)	Rat; acute contusion injury	Cold saline (8°C) infusion Duration: 6 h Timing: ~20 min postinjury	1 d postinjury	Edema, microvascular perfusion, leukocyte rolling/adhesion Neutrophils and macrophages Desmin expression

CSA, cross-sectional area; TGF, transforming growth factor

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Table 4. Summary of physiological and molecular responses, acute and chronic adaptations to treatments that enhance or dampen exercise-induced hormesis in skeletal muscle.

	Treatments that dampen hormesis				Treatments that enhance hormesis				
	Cryotherapy	NSAIDs	Antioxidant supplementation		Carbohydrate restriction		Heat stress		Blood flow restriction
Physiological rationale	Analgesia ↓ Muscle blood flow ↓ Inflammation ↑ Hydrostatic pressure	Analgesia ↓ Inflammation	↓ Oxidative stress		↑ Metabolic stress		↓ Muscle breakdown		↑ Metabolic stress ↑ Oxidative stress ↑ Blood pooling
Cells and signalling molecules upregulated	TGF-β	IL-6 MCP-1 Cyclooxygenase 2			AMPK ACC p53 PGC-1α CS	SDH HAD COXIV PDK4	Macrophages HSPs MyoD Myogenin mTOR	CS PGC-1α p38 MAPK p70S6K	Pax7 AMPK MAPK HSPs
Cells and signalling molecules downregulated	Neutrophils Macrophages IGF-1 Pax7	Prostaglandins ERK/RSK/MNK p70S6K/rpS6 Leukotrienes Resolving mediators	p38 MAPK ERK AMPK IL-6 NFκB	PGC-1α Tfam COX SOD			Macrophages NFκB AMPK ACC		
Acute effects	↓ Soreness	Sorness? ↔ Inflammation ↓ Protein synthesis ↓ Satellite cells			↓ SR Ca^{2+} release rate ↑ Protein breakdown		↓ Loss of strength* ↓ Soreness* ↓ Swelling ↑ Range of motion*		↑ Loss of strength ↑ Soreness ↑ Swelling
Chronic effects	↓ Fibre CSA ↑ Fibrosis ↓ Strength	Young healthy ↔ muscle mass?	↓ Antioxidant enzymes		↑ Mitochondrial enzymes ↑ Fat oxidation		↑ Mitochondrial enzymes ↑ Respiratory chain protein content		↑ Hypertrophy

	↔ strength?	↔ Performance
	Elderly	
	↑ muscle mass	
	↑ strength	

Abbreviations: TGF, transforming growth factor; MCP, monocyte chemotactic protein; AMPK, adenosine monophosphate activated protein kinase; ACC, acetyl-CoA-carboxylase; PGC, peroxisome proliferator-activated receptor coactivator; CS, citrate synthase; SDH, succinate dehydrogenase; HAD, hydroxyacyl-CoA-dehydrogenase; COX, cytochrome oxidase; PDK, pyruvate dehydrogenase kinase; HSP, heat shock protein; Pax, paired box protein; mTOR; mammalian target of rapamycin; Mnk, MAPK-interacting kinase; RSK, p90 ribosomal S6 kinase; rpS6, ribosomal S6 kinase; Tfam, mitochondrial transcription factor A; SOD, superoxide dismutase; CSA, cross-sectional area. ↔ no change. * conflicting evidence for an increase/decrease or no change.

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